REMARKS

Claims 1-4, 11-14 and 16-24, 41, 42, 45, 47, 49, and 59 are pending in the application. Claims 19-21 and 47 are withdrawn from consideration as being drawn to non-elected inventions. Applicant notes that claims 2 and 3 are incorrectly listed as withdrawn on the Office Action Summary page, but have been rejoined for examination. By this amendment, claims 1, 3, 4, 11, 12, 13, 14, and 41 have been amended, new claim 59 has been added, and claims 5-10, 15, 25-40, 43, 44, 46, 48, and 50-58 have been canceled without prejudice or disclaimer. Claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 15-18, 22-24, 41, 42, and 45 are under active consideration.

Claim 1 has been amended to make explicit that the fusion protein comprises sequences that are not in the order in which they occur naturally in the HCV polyprotein. Support for the amendment can be found in the specification, for example, at page 4, lines 8-11; and page 24, lines 3-20. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Claims 1, 11, and 12 have been amended to remove the term "derived" from the claims. Applicant is amending the claim solely to obtain expeditious allowance of the instant application and not for reasons related to patentability. Entry of the amendments is respectfully requested.

Claims 3, 4, and 41 have been amended to remove the term "optionally" from the claims. Entry of the amendments is respectfully requested.

Claim 12 has been amended to recite "the fusion is derived from a different isolate than the modified NS3 polypeptide." Applicant is amending the claim solely to obtain expeditious allowance of the instant application and not for reasons related to patentability. Entry of the amendment is respectfully requested.

Claim 13 has been amended to make explicit that at least one of the polypeptides present in the fusion is from a different isolate than the modified NS3 polypeptide. Support for the amendment can be found in the specification, for example, at page 3, lines 11-14; page 23, lines 26-28; and page 24, lines 21-22. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Claims 13 and 14 have been amended to recite "consisting of." Applicant is amending the claim solely to obtain expeditious allowance of the instant application and not for reasons related to patentability. Entry of the amendments is respectfully requested.

Claims 13 and 14 have been amended, and claims 5-10, 25-40, 43, 44, 46, 48, and 50-58 have been canceled without prejudice or disclaimer in order to remove non-elected subject matter. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Support for new claim 59 can be found in the specification, for example, at page 3, lines 18-29; page 24, lines 3-21; and Example 1. Entry of the new claim is respectfully requested.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Restriction Requirement

Applicants affirm the election with traverse of Group V, which corresponds to claims 4, 13(b) and 14(b), directed to a fusion protein comprising a modified NS3 polypeptide, an NS4 polypeptide, an NS5a polypeptide, an NS5b polypeptide, and optionally a core polypeptide. Applicants thank the Examiner for rejoining Group III, which corresponds to claims 2 and 15, drawn to a fusion protein comprising a modified NS3 polypeptide and an HCV polypeptide other than NS3, wherein the modification comprises an amino acid substitution corresponding to His-1083, Asp-1105 and/or Ser-1165; and Group IV, which corresponds to claims 3, 13(a) and 14(a), directed to a fusion protein comprising a modified NS3 polypeptide, an NS4 polypeptide, an NS5a polypeptide, and optionally a core polypeptide; and new claims 41, 42, 45, and 49.

Rejoinder

Applicants request that claims 19-21 and 47, drawn to methods of using the fusion proteins of Groups III-V, be rejoined per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants request that claims 19-21 and 47 be rejoined and examined upon allowance of any of the claims drawn to the fusion proteins of Groups III-V.

Priority

The Office Action states that the subject matter of claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 15-18, 22-24, 41, 42, and 45 is not entitled to the benefit of priority of U.S. Application Serial No. 09/721,479 filed November 22, 2000 and provisional U.S. Application Serial No. 60/167,502 filed November 24, 1999; therefore, "the earliest date to which Applicant may claim priority is July 2, 2002" (Office Action, page 3). Applicants respectfully disagree. The provisional U.S. Application Serial No. 60/167,502 describes "a mutant polypeptide, comprising at least portions of NS3, NS4, or NS5, comprising a deletion in, or mutation of, the NS3 protease active site region to render the protease non-functional" (see specification at page 11, lines 22-23). U.S. Application Serial No. 09/721,479 describes an HCV polypeptide comprising a polypeptide having a mutation in the catalytic domain of NS3 that functionally disrupts the catalytic domain and states explicitly that "the mutation can be, for example, a deletion, or a substitution mutation" (see specification at page 4, lines 11-13). Nevertheless, Applicants do not need to rely on the earlier priority dates to overcome the cited art.

Objection to the Specification

The specification is objected to on the grounds that amino acid sequences are present in the figures and on page 45, line 21 that are not identified by appropriate SEQ

ID NO identifiers. Applicant has amended the specification at page 45 to include sequence identifiers as required. In addition, the "Brief Description of the Figures" at page 8 has been amended to list the appropriate sequence identifiers for sequences shown in the figures. Support for these amendments can be found in the sequence listing at pages 1-19. No new matter is added by these amendments and entry of these amendments is respectfully requested. Withdrawal of the objection to the specification is therefore respectfully requested.

Objection to the Claims

Claim 12 has been amended as suggested by the Examiner to recite "the fusion is from a different isolate than the modified NS3 polypeptide." Withdrawal of the objection to the claim is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 17, 18, and 22-24 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Office Action, page 4).

(a) The Office Action alleges that "the term, 'derived' does not impart any clear or definite meaning to the polypeptide. The metes and bounds of the polypeptide from a region of the HCV polyprotein or isolate cannot be determined because Applicant has not set forth the parts that are retained from the original HCV polyprotein or isolate from which the polypeptide is derived." (Office Action, page 4.) Applicant notes that the definition of the term derived appears in the specification, for example, at page 10. Nevertheless, in order to expedite prosecution, claims 1, 11, and 12 have been amended to remove the term derived.

(b) The Office Action alleges that it is unclear how the closed language "consisting essentially of" in the claims allows for a variable number of amino acid substitutions that do not affect the product (Office Action, page 4). To expedite prosecution, claims 13 and 14 have been amended to recite "consisting of."

For at least these reasons, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 102

Claim 15 has been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the reference of Grakoui et al. (1993) J. Virology 67:2832-2843. In particular, the Office Action alleges:

> Grakoui discloses the substitution of alanine for His-1083, Asp-1107 and Ser-1165 in HCV NS3, resulting in uncleaved NS domains. This activity qualifies as inhibited protease activity (abstract). While the substitution of alanine for Asp-1107 is not Asp-1105 (as claimed), position 1107 corresponds to the HCV-1 polyprotein, thus meeting the limitation of the claim. With regard to the limitation pertaining to the NS3 polypeptide being present in an HCV fusion protein and having inhibited activity, Grakoui's modified NS3 polypeptide(s) is expected to have inhibited activity when present in a fusion protein. Inhibited activity is expected because Grakoui found that the modified NS3 does not cleave other non-structural polypeptides, and Grakoui found that NS3 is not dependent on NS2 for its protease activity (abstract). The location (within a fusion protein) of the modified NS3 is not expected to change its inhibited protease activity due to the amino acid substitution of His-1083, Asp-1107 or Ser-1165.
> (Office Action, page 5.)

Applicants respectfully traverse the rejection under 35 U.S.C. § 102(b) on the following grounds.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102, "the reference must teach every aspect of the claimed invention either explicitly or implicitly." M.P.E.P. § 706.02. Applicants respectfully submit that the reference of Grakoui et al. does not teach or suggest all aspects of the Applicants' invention, either explicitly or implicitly.

The reference of Grakoui et al. does not disclose an HCV fusion protein comprising sequences that are not in the order in which they occur naturally in the HCV polyprotein. Grakoui also fails to disclose an HCV fusion protein comprising a modified NS3 polypeptide in combination with a core domain or portion thereof that lacks the intervening regions (*i.e.*, E1, E2, p7, NS2) naturally occurring in the HCV polyprotein. Nor does Grakoui disclose fusion proteins, wherein at least one of the polypeptides

present in the fusion is from a different HCV isolate than the modified NS3 polypeptide. Therefore, Grakoui fails to teach all the limitations of the claims.

For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 15-18, 22-24, 41, 42, 45, and 49 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Paliard et al. (WO 01/30812 A2) in view of the reference of Houghton et al. (U.S. 5,371,017) and Grakoui et al. (1993) J. Virology 67:2832-2843. In particular, the Office Action alleges:

> It would have been obvious to incorporate Houghton's teachings and Grakoui's teachings into the fusion protein of Paliard. One would have been motivated to render the protease (NS3) non-functional in order to avoid cleavage of polyprotein, as taught by Houghton (col.3, lines 29-34, and col. 14, lines 32-48). One would have been motivated to substitute the amino acids taught by Grakoui because Houghton discloses that certain substitutions result in the inhibition or ablation of protease function. One would have had a reasonable expectation that Paliard's fusion protein would have worked with Houghton's NS3 amino acid substitution and Grakoui's substitution, because Grakoui demonstrates that the substitutions result in inhibited or non-existent protease activity."
> (Office Action, page 8).

Applicants respectfully traverse the rejections under 35 U.S.C. § 103 on the following grounds.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02.

Applicants submit that the cited references do not disclose or suggest all the limitations of the present invention. Thus, a *prima facie* case of obviousness has not been presented by the Office, and the cited combination is based on impermissible hindsight reconstruction.

As mentioned above, Grakoui et al. fail to describe or suggest HCV fusion proteins comprising sequences that are not in the order in which they occur naturally in the HCV polyprotein. The secondary references also fail to teach or suggest such fusion proteins.

Houghton et al. (5,371,017) fail to describe or suggest HCV fusion proteins comprising a modified NS3 polypeptide fused to other HCV sequences (see col. 6, lines 63-67). Palliard et al. fail to describe or suggest HCV fusion proteins having an NS3 polypeptide modified such that protease activity is inhibited. Nor do Palliard et al. describe or suggest fusions containing the core domain or a portion thereof.

Thus, the references do not disclose or suggest all the limitations of the present invention, and the Examiner has not met the burden of establishing a *prima facie* case of obviousness. In the absence of some teaching or suggestion in the cited references concerning immunogenic fusion proteins comprising a modified NS3 polypeptide and other HCV sequences, described in the present application, the Examiner has presented no more than an improper hindsight reconstruction of the present invention. As stated by the Court of Appeals for the Federal Circuit *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103. For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicant submits that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

Michael J. Moran
Chiron Corporation
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097
Tel: (510) 923-2969
Fax: (510) 655-3542

Respectfully submitted,

Date: September 14, 2005

By: Jenny Buchbinder

Jenny Buchbinder, Ph.D.
Registration No. 48,588
(650) 354-3383

CHIRON CORPORATION
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097